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**Sent:** Wednesday, November 16, 2005 11:37 AM  
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**Document Citation**

**Title:** Production of cytokines by polymorphonuclear neutrophils

**Authors:** Cassatella, Marco A.

**Source:** Neutrophils: New Outlook for Old Cells (1999); 151-229. Editor(s): Gabrilovich, Dmitry I. Publisher: Imperial College Press, London, UK.  
CODEN: 67WVAQ

**Corporate Source:** Istituto di Patologia Generale, Verona, 37134, Italy

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From: Haddad, Maher  
Sent: Wednesday, November 16, 2005 11:24 AM  
To: STIC-ILL  
Subject: 10/648,136

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Barone D (Reprint); Kennedy M; Sivakumar P V; Brown S; Mohler K

Role of CD30/CD30L interactions in autoimmune disease. ARTHRITIS AND RHEUMATISM, (SEP 2000)  
Vol. 43, No. 9, Supp. [S], pp. S85-S85. MA 109. ISSN: 0004-3591.

Thanks\_Maher

ROLE OF CD30/CD30L INTERACTIONS IN AUTOIMMUNE DISEASE. Dauphine Barone, Mary Kennedy, P V Sivakumar, Sandra Brown, Kendall Motter Seattle, WA

Extensive preclinical and clinical studies have documented the role of TNF in autoimmune diseases, esp. rheumatoid arthritis. We have examined the role of another member of the TNF ligand family, CD30L, in autoimmune disease. Recent studies have suggested that CD30L limits the expansion and subsequent pathogenesis of autoimmune CD8+ T cells (Heath, et al. 1999, Immunol. Rev. 162:23). However, the role of CD30L in regulating autoimmune CD4+ T cells has not been determined. In order to examine the role of CD30L in autoimmune disease, we generated a monoclonal antibody (M15) to mouse CD30L that blocks its interaction with CD30. As expected, M15 stains activated, but not resting, murine T cells. We initially examined the effect of M15 on immune responses in vitro. M15 had no effect on in vitro proliferation or cytokine production (IL-4 or IFN $\gamma$ ) of spleen cells or T cell clones in response to stimulation with either antigen (OVA) or anti-CD3. In contrast, administration of M15 in vivo significantly attenuated collagen-induced arthritis. DBA/1 mice were injected with type II collagen in adjuvant on D0 and D21. Treatment with M15 (0.15 - 150  $\mu$ g/d, ip), or control protein (IgG) was initiated on D21 and continued for 14d. Mice treated with M15 at doses of 50  $\mu$ g/d or greater demonstrated a significant decrease in disease incidence and severity. These results suggest that treatment with CD30L antagonists may be beneficial in autoimmune disease and that the control of autoimmune CD8+ and CD4+ T cell responses may be differentially regulated by CD30L. Additional studies are in progress to determine the mechanism of action of M15 in vivo.

Disclosure: Authors are full time employees of Immunex Corporation.

## 110

IL-7 PROMOTES DIRECT AND IL-12-DEPENDENT STIMULATION OF TH1 ACTIVITY IN JOINTS OF PATIENTS WITH RHEUMATOID ARTHRITIS. J AG van Roon, C AFM Glandemans, F PJG Labefer, J WJ Blijlsma Utrecht, The Netherlands

In RA patients, IL-7 is found to be increased in serum and increased production by fibroblastlike synovial cells has been shown. IL-7 is able to stimulate proliferation of synovial fluid mononuclear cells (SFMC). This effect of IL-7 in terms of Th1 and Th2 cell activity as well as TNF $\alpha$  production was studied.

SFMC (n=7) from RA patients were treated with IL-7 (0.01-1 ng/ml) or anti-IL-7 for 5 days. Anti-IL-12 was used to test the interference of IL-12. CD4+ T cell cytokine production (IFN $\gamma$  and IL-4 as well as TNF $\alpha$  by ELISA and FACS analysis) was assessed upon CD3/28 restimulation. In addition synovial memory CD4+ T cells (n=3) were isolated by MACS cell sorting to test direct effects of IL-7 in cultures under CD3/CD28 co stimulation.

Neutralisation of (potentially) endogenously produced IL-7 by adding anti-IL-7 did not change T cell cytokine profiles. Addition of IL-7, primed T cells in the context of SFMC, for IFN $\gamma$  production dose dependently up to 1250% (p<0.01), but not for IL-4 production (max +37%, ns). TNF $\alpha$  production was doubled (p<0.01). Neutralization of IL-12 in IL-7 stimulated SFMC cultures halved IFN $\gamma$  production (p<0.01), and increased IL-4 production (93%, p<0.01), but did not change TNF $\alpha$  production. (The effect of anti-IL-12 on IL-7 induced IFN $\gamma$  production could also be obtained by IL-10 addition.) Also for isolated CD4+ T cells, IFN $\gamma$  production was significantly enhanced by IL-7 addition (from 8.6 to 42.3 ng/ml, p<0.05). TNF $\alpha$  increased more than 10 fold (2.5 to 27.6 ng/ml, p<0.05). IL-4 was enhanced under these conditions as well.

The present study confirms earlier reports that IL-7 is not produced in significant amounts by SFMC, and demonstrates that IL-7, which is produced by synovial fibroblasts, can very potently prime for IFN $\gamma$  and TNF $\alpha$  production by CD4+ T cells, both directly and via induction of IL-12. The significant production of IFN $\gamma$  and TNF $\alpha$  by T cells remaining in the absence of IL-12 indicates that IL-7 may importantly contribute to joint inflammation in RA.

Disclosure: This study was supported by the Dutch League against Rheumatism

## 111

IFN  $\gamma$  PRODUCTION BY PATIENTS WITH EARLY RHEUMATOID ARTHRITIS (RA <5 YEARS) UPON IN-VITRO CHALLENGE WITH BACTERIAL hsp60 PEPTIDES. Francesca Giannoni, Rodrigo T Samodai, Joellen Barnett, Eileen Quintela, Rowena Aguilar, Willem van Eden, Berent J Prakken, Salvatore Albani La Jolla, CA and The Netherlands

We have recently shown that human and bacterial heat shock protein (hsp60) can be targets of autoimmune T cell responses. We have previously identified potential hsp60 peptide epitopes that are reactive in children with JRA. Since hsp60 contain conserved sequences, it would be interesting to study the association of these same peptides in similar autoimmune dysfunction as Rheumatoid Arthritis.

We analyzed 6 stretches of mycobacterial hsp60 of varying sequences between 23 to 38 amino acids in length and encompassing all major T cell epitopes of mycobacterial hsp60 in Adjuvant Arthritis. Applying a method in predicting potential pan-DR binding sites on a given protein sequence (Epiimmune, La Jolla Ca.). We tested seven 15-mer synthetic hsp60 peptide analogs using PHMC of 15 early RA patients (<5 years) and 4 non-RA healthy controls in a single-pulsed 5 day culture. Quantitative measurements for IFN $\gamma$  from supernatant by capture ELISA and by intracellular staining showed correlative cytokine production in all the peptides tested. More than half of the peptides tested yielded higher responses among the RA patients than the healthy controls. These preliminary results suggest association of these peptides with RA and may potentially be targets for immune therapy.

Disclosure:

## 112

HIGH INTERLEUKIN-16 PROTEIN SECRETION FROM EX VIVO RHEUMATOID SYNOVIAL MEMBRANE CULTURES. Katherine M Farmer, Ian Porter, Marissa Lasserre, C Soon Lee, John P Edmonds, Bruce W Kirkham Sydney, NSW, Australia and London, United Kingdom

**Objective:** Interleukin-16 (IL-16) is a CD4+ cell-specific chemotactic factor produced predominantly by CD8+ T cells, but also by mast cells, eosinophils and fibroblasts. IL-16 induces energy and suppresses antigen-induced proliferation of CD4+ T cells. High synovial fluid IL-16 levels has recently been reported in patients with rheumatoid arthritis (RA). We measured IL-16 protein secretion by ex vivo RA synovial membrane (SM) cultures and compared them with other secreted cytokines, and clinical and laboratory measures of disease activity.

**Methods:** SM biopsies were obtained from patients with RA (n=34) undergoing arthroscopy and cultured as either tissue pieces (SM biopsy culture) or collagenase digested cell suspensions (SM cell culture). Supernatants were collected at various time points over 6 days and the amount of secreted IL-16, IL-10, IL-18, TNF $\alpha$  and IFN $\gamma$  protein was measured by ELISA. ESR, CRP, RF, and swollen joint count were recorded for a subset of patients. Spearman rank correlations with p<0.05 are reported.

**Results:** IL-16 was produced by all RA SM biopsy and cell cultures at higher quantities compared to the other cytokines. Kinetic studies in the cell cultures showed that IL-16 production continued at a similar level over 6 days. The range of IL-16 secretion from SM cell cultures (n=15) was 134 to >4000 pg/ml. Positive correlations were found between IL-16 and IL-18 (n=10, p=0.0022, r=0.8667), IL-10 (n=11, p=0.0112, r=0.7455) and ESR (n=5, p=0.0255, r=0.7395).

SM biopsy culture (n=20) IL-16 secretion ranged from 316 to >4000pg/ml (883 to 19523 pg/ml/100mg for quantified values). Positive correlations were found between secreted IL-16 pg/ml and IL-10 (n=19, p=0.0011, r=0.6897), and TNF $\alpha$  (n=19, p=0.0101, r=0.8745). A negative correlation was found between secreted IL-16 pg/ml and swollen joint count (n=9, p=0.0311, r=-0.7333).

**Conclusion:** This is the first report of secreted IL-16 protein production by ex vivo SM cultures from RA patients. The very high levels found in some patients may explain some of the downregulation of T cell function in the RA synovium. These data suggest IL-16 may play an important role in the pathophysiology of RA.

Disclosure:

## 113

ANALYZING GENE EXPRESSION BY IMMUNOREGULATORY CYTOKINES THROUGH THE USE OF MICROARRAYS. Tammy P Cheng, Hyun-Jong Ahn, Jerome Galon, Massimo Gadina, Roberto Bomprezzi, Michael Birner, Jeffrey M Trent, John J O Shea Bethesda, MD

Cytokines play critical roles in immunoregulation. While cytokines such as IL-2 and IL-7 promote lymphocyte growth and homeostasis, IL-12 and IL-4 are important, respectively, for the development of Th1 and Th2 cells, a dichotomy implicated in the pathogenesis of diseases ranging from rheumatoid arthritis to asthma. Since relatively little is known about the gene expression changes effecting cytokine action, we sought to delineate cytokine-inducible genes via cDNA glass-slide microarrays and used bioinformatic tools to compare and in contrast genomic expression patterns by various immunoregulatory cytokines.

Total RNA was extracted from human peripheral blood mononuclear cells stimulated with the  $\gamma$ c cytokines (IL-2, IL-4, IL-7 and IL-15), IL-12, IL-18 and IFN $\gamma$  for 7 hours in multiple parallel experiments. cDNA probes, reverse transcribed from pooled RNA samples, were then labeled with either Cy3 or Cy5 fluorescent tags. Expression changes of 6,800 genes between the cytokine stimulated and unstimulated cell populations were analyzed on each array. We delineated 496 genes significantly regulated by one or more cytokine conditions. Furthermore, using Pearson Correlation analysis, a clustering algorithm generated a dendrogram based on overall expression profile similarities. IL-18 was found to have the most dissimilar genome expression profile from the other cytokines tested, a finding consistent with the fact that IL-18 regulates gene transcription mainly via NF- $\kappa$ B activation, in contrast to the other cytokines which act via the STAT family of transcription factors. Furthermore, among the  $\gamma$ c cytokines, IL-4 demonstrated the most distinct expression profile whereas the genomic patterns of IL-2 and IL-15 clustered closely together. Lastly, the combination of IL-12 and IL-18 regulated an overall expression profile distinct from that of either cytokine alone, consistent with the highly synergistic action of IL-12 and IL-18. Sixty-eight genes were identified as dramatically induced by the combination of IL-12 and IL-18, but not by either cytokine alone.

Microarrays are a powerful technology for comparing genome-wide expression changes. Furthermore, these findings demonstrated the robustness of the clustering algorithm in distinguishing biologically significant trends based on genome expression profile alone. By providing novel insights into the molecular bases of cytokine action, microarray analysis may enable us to better understand the pathogenesis of immune-mediated diseases.

Disclosure:

## 114

MULTIPLE SIGNALING PATHWAYS ACCOUNT FOR THE SYNERGISTIC INDUCTION OF MMP-1 BY INTERLEUKIN-1 IN COMBINATION WITH ONCOSTATIN M IN CHONDROCYTES. A D Rowan, J B Catterall, S Carrere, P JT Koshy, W D Shingleton, B A Degnan, J Rutter, C E Hinrichsenhoff, T E Cawston

**AIMS:** Interleukin-1 (IL-1) in combination with oncostatin M (OSM) cause the synergistic induction of matrix metalloproteinase-1 (MMP-1) in human chondrocytes [1]. This study aims to identify the intracellular components involved in this induction and determine if modulation of cell surface receptors accounts for this effect.

**METHODS:** A human chondrocyte line, T/C28A4, was used and surface receptors assessed using flow cytometry, Northern blotting and RT-PCR. Effects of IL-1 + OSM stimulation on the transcriptional activation of the MMP-1 promoter were evaluated using transient transfections with MMP-1 promoter/luciferase constructs [2]. Binding of nuclear factors to the MMP-1 promoter was determined by gel mobility shift and supershift assays.

**RESULTS:** A rapid synergistic induction of MMP-1 was seen with IL-1 + OSM by 4h. No significant modulation of the surface receptors gp130, OSMR $\beta$  or IL-1RI was observed following stimulation. Transient transfections indicated that the proximal (-517/+63) region of the MMP-1 promoter was sufficient to support a synergistic transcriptional activation by IL-1 + OSM, and that removal of a potential STAT binding element had no effect on the activation. Binding of AP-1 complexes, containing c-fos in particular, to the promoter was shown, whilst an indirect role for STAT proteins was found following OSM stimulation. Specific inhibitors of p38 and ERK mitogen-activated protein kinases (MAPK) reduced or blocked the synergistic activation of MMP-1.

**CONCLUSIONS:** Modulation of cell surface receptors does not account for the synergistic activation of MMP-1 in human chondrocytes stimulated with IL-1 + OSM. Rather, interplay between several signal transduction pathways including the JAK/STAT, p38 and ERK MAPK pathways is involved. A role for AP-1 binding has been demonstrated, and that STAT-induced c-fos and changes in the activation state or composition of AP-1 complexes lead to this synergistic activation.

REFERENCES 1. Cawston et al. Arthritis Rheum 1998;41:1760-1771.

2. Rutter et al. J Cell Biochem 1997;66:322-336.

Disclosure:

## WEST Search History





DATE: Wednesday, November 16, 2005

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<input type="checkbox"/>	L2	kit adj22 (microsphere\$ or microparticles or polystyren or magnetic or paramagnetic) adj22 antibod\$	36
<input type="checkbox"/>	L1	Elisa adj22 streptavidin adj22 horseradish	7

END OF SEARCH HISTORY

L5 ANSWER 14 OF 100 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:443007 CAPLUS

DOCUMENT NUMBER: 131:335417

TITLE: Production of cytokines by polymorphonuclear neutrophils

AUTHOR(S): Cassatella, Marco A.

CORPORATE SOURCE: Istituto di Patologia Generale, Verona, 37134, Italy

SOURCE: Neutrophils: New Outlook for Old Cells (1999), 151-229. Editor(s): Gabrilovich, Dmitry I. Imperial College Press: London, UK.

CODEN: 67WVAQ

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review with 229 refs. on the production and regulation of cytokines by neutrophils in health and disease. Topics discussed include chemokines, interleukins, growth related gene product- $\alpha$  and GRO $\beta$ , IP-10, MIP-1 $\alpha$ , monocyte chemotactic proteins, tumor necrosis factor- $\alpha$ , CD30 ligand, IL-1RA, transforming growth factor, interferon, inflammatory bowel disease, autoimmune diseases, sepsis, and viral infections.

REFERENCE COUNT: 231 THERE ARE 231 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L5 ANSWER 15 OF 100 CIN COPYRIGHT 2005 ACS on STN

AB Immunex Corp.'s (IMNX, Seattle, Wash.) researchers published the identification and characterization of vCD30, a virally encoded CD30 homolog. In culture, vCD30 bound CD153 (CD30 ligand) and inhibited CD30-CD153 interactions, leading the authors to suggest that CD30 could be used as a target in inflammatory and autoimmune diseases.

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L5 ANSWER 15 OF 100 CIN COPYRIGHT 2005 ACS on STN

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L4 ANSWER 16 OF 40 CANCERLIT on STN

ACCESSION NUMBER: 97605333 CANCERLIT

DOCUMENT NUMBER: 97605333

TITLE: Human eosinophils (EOs) express functional CD30 ligand and stimulate proliferation of Hodgkin's disease cells (Meeting abstract).

AUTHOR: Pinto A; Aldinucci D; Zagonel V; Gloghini A; Juzbasic S; Perin V; Degan M; Improta S; Sacco C; Canale V; Gattei V; Monfardini S; Gruss H J; Carbone A

CORPORATE SOURCE: Centro di Riferimento Oncologico, IRCCS, 33081, Aviano, Italy.

SOURCE: Proc Annu Meet Am Soc Clin Oncol, (1996) 15 A1267.  
ISSN: 0732-183X.

DOCUMENT TYPE: (MEETING ABSTRACTS)

LANGUAGE: English

FILE SEGMENT: Institute for Cell and Developmental Biology

ENTRY MONTH: 199703

ENTRY DATE: Entered STN: 19980417

Last Updated on STN: 19980417

AB The presence of a prominent eosinophilia in Hodgkin's disease (HD) tissues was first described one century ago and it is now well established that EOs infiltration and/or EOs degranulation products can be detected in up to 89% of nodular sclerosis and mixed cellularity HD cases.

Eosinophilia in HD is partly due to synthesis of recruiting cytokines (IL-5, GM-CSF) by Hodgkin's H and Reed-Sternberg (RS) cells. Despite the extensive infiltration in HD tissues, the possible role of EOs in the regulation of H-RS cells growth has not been addressed so far. On the other hand, some evidence suggests that tumor growth in HD may depend on a network of cytokine- and cell contact-mediated interactions among H-RS cells and surrounding reactive cells. Among the surface molecules mediating such interactions, CD30 has been recently characterized as a transmembrane growth factor receptor able to transduce proliferation signals in H-RS cells upon engagement by a specific ligand (CD30L). To clarify the biologic significance of eosinophilia in HD, EOs from healthy donors and patients with HD or primary hypereosinophilia (PH) were isolated to 95-98% purity and studied for CD30L expression by staining with a monoclonal antibody (M80) generated against recombinant CD30L or a CD30-Fc fusion protein, and RT-PCR. Our results indicate that purified EOs from patients and normal donors showed a strong constitutive expression of surface CD30L and display mRNA encoding for CD30L. Interestingly, EOs from peripheral blood and pleural effusions of patients with active HD and with PH showed a higher constitutive expression of CD30L as compared to healthy subjects. Accordingly, CD30L expression was consistently detected by immunohistochemistry on tissue EOs from reactive and HD-involved lymph nodes. In addition, cytokines regulating EOs proliferation and activation (IL-5, IL-3, GM-CSF) were able to enhance the cellular density of CD30L on cultured EOs. IL-5 displayed a higher capability to up-regulate surface expression of CD30L (219% of unstimulated EOs) as compared to IL-3 (127%) and GM-CSF (198%), even though the maximal increase of CD30L specific fluorescence (350% of controls) was obtained by a combination of GM-CSF and IL-3. To examine whether native CD30L on human eosinophils was functionally active in promoting the growth of cultured H-RS cells, titrations of paraformaldehyde-fixed pure EOs were co-cultured with the HD-derived cell line HDLM-2. EOs induced a dose-dependent proliferation of HDLM-2 cells. These proliferative effects were highly specific and CD30L-mediated since they could be completely blocked by soluble CD30-Fc fusion protein. Our results suggest for the first time that eosinophils in HD may not simply represent 'innocent' bystanders but could rather participate to the cellular network promoting H-RS cells growth through a CD30L/CD30-dependent mechanism.

(C) American Society of Clinical Oncology 1997.

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proliferation signals in H-RS cells upon engagement by a specific ligand (CD30L). To clarify the biologic significance of eosinophilia in HD, EOs from healthy donors and patients with HD or primary hypereosinophilia (PH) were isolated to 95-98% purity and studied for CD30L expression by staining with a monoclonal antibody (M80) generated against recombinant CD30L or a CD30-Fc fusion protein, and RT-PCR. Our results indicate that purified EOs from patients and normal donors showed a strong constitutive expression of surface CD30L and display mRNA encoding for CD30L. Interestingly, EOs from peripheral blood and pleural effusions of patients with active HD and with PH showed a higher constitutive expression of CD30L as compared to healthy subjects. Accordingly, CD30L expression was consistently detected by immunohistochemistry on tissue EOs from reactive and HD-involved lymph nodes. In addition, cytokines regulating EOs proliferation and activation (IL-5, IL-3, GM-CSF) were able to enhance the cellular density of CD30L on cultured EOs. IL-5 displayed a higher capability to up-regulate surface expression of CD30L (219% of unstimulated EOs) as compared to IL-3 (127%) and GM-CSF (198%), even though the maximal increase of CD30L specific fluorescence (350% of controls) was obtained by a combination of GM-CSF and IL-3. To examine whether native CD30L on human eosinophils was functionally active in promoting the growth of cultured H-RS cells, titrations of paraformaldehyde-fixed pure EOs were. . . the HD-derived cell line HDLM-2. EOs induced a dose-dependent proliferation of HDLM-2 cells. These proliferative effects were highly specific and CD30L-mediated since they could be completely blocked by soluble CD30-Fc fusion protein. Our results suggest for the first time that eosinophils. . . may not simply represent 'innocent' bystanders but could rather participate to the cellular network promoting H-RS cells growth through a CD30L/CD30-dependent mechanism.

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(FILE 'HOME' ENTERED AT 10:53:48 ON 16 NOV 2005)

FILE 'DISSABS, IMOBILITY, AGRICOLA, AQUASCI, BIOTECHNO, COMPENDEX,  
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PAPERCHEM2, PASCAL, POLLUAB, SOLIDSTATE, ADISCTI, ADISINSIGHT, ADISNEWS,  
ANABSTR, ANTE, AQUALINE, BIOBUSINESS, BIOCOMMERCE, ' ENTERED AT 10:54:18  
ON 16 NOV 2005

L1 2652 S CD30L OR CD153 OR (CD30 (A) LIGAND)  
L2 181 S L1 (S) (AUTOIMMUNE OR LUPUS OR ARTHRITIS OR SCLEROSIS OR DER  
L3 140 DUP REM L2 (41 DUPLICATES REMOVED)  
L4 40 S L3 (S) (ANTI OR ANTIBOD? OR MAB)  
L5 100 S L3 NOT L4

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USPATFULL, WPIDS' ENTERED AT 11:26:33 ON 16 NOV 2005

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USPATFULL, WPIDS' ENTERED AT 11:34:13 ON 16 NOV 2005

FILE 'STNGUIDE' ENTERED AT 11:34:20 ON 16 NOV 2005

ACCESSION NUMBER: 2002:104376 SCISEARCH

THE GENUINE ARTICLE: 498EB

TITLE: Beneficial effect of an antibody to  
CD30L in autoimmune disease.

AUTHOR: Barone D (Reprint); Kennedy M; Alcorn D; Majeskey K; Brown  
S; Sivakumar P V; Mohler K

SOURCE: ARTHRITIS AND RHEUMATISM, (SEP 2001) Vol. 44, No. 9, Supp.  
[S], pp. S241-S241. MA 1132.

ISSN: 0004-3591.

PUBLISHER: WILEY-LISS, DIV JOHN WILEY & SONS INC, 111 RIVER ST,  
HOBOKEN, NJ 07030 USA.

DOCUMENT TYPE: Conference; Journal

LANGUAGE: English

REFERENCE COUNT: 0

ENTRY DATE: Entered STN: 15 Feb 2002

Last Updated on STN: 15 Feb 2002

TI Beneficial effect of an antibody to CD30L in  
autoimmune disease.